Reduced exercise capacity is associated with reduced nitric oxide production after heart transplantation

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Despite subjective functional improvement and improvement in quality of life, heart transplant recipients demonstrate a persistent reduction in exercise capacity. Central factors, such as cardiac dysfunction and chronotropic insufficiency, likely participate in this limitation, but numerous studies underlined the role of peripheral factors.[1] Nitric oxide (NO), mainly produced in the endothelium, is a major component involved in both basal and exercise vascular tone, and flow-mediated release of NO is thought to be important for exercise-induced vasodilation. Interestingly, an exercise-induced increase in circulating nitrates and nitrites (NOx), the stable end product reflecting NO production, has recently been observed and was associated with physical fitness in healthy human subjects.[2,3] Furthermore, supplementation with the NO precursor L-arginine enhanced endothelium-dependant vasodilation and exercise capacity in patients with heart failure.[4] We therefore investigated whether impaired NO release might participate in exercise limitation after heart transplantation.

Method and Results

Plasma NOx values were determined by the colorimetric method on the basis of the Griess reaction before, at 70% of peak, at peak, and at 10, 30, and 60 minutes of recovery during a graded maximal bicycle exercise in 8 heart transplant recipients and 8 age- and weight-matched healthy control subjects. All subjects were in sinus rhythm and free of cardiac symptoms. The mean time elapsed since transplantation was 3 years, and heart transplant recipients, free of rejection, were undergoing their usual triple immunosuppressive therapy. The study was approved by the university review board for human studies, and each subject gave informed consent.

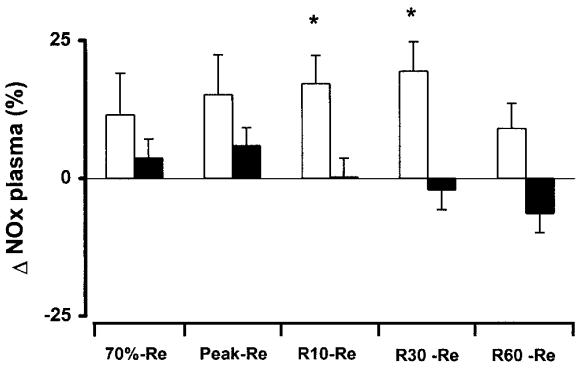

Figure 1. Time course of NOx changes in response to maximal ergocycle exercise in healthy subjects *(open bars)* and in heart transplant recipients *(filled bars)*. *70%-Re*, Submaximal exercise at 70% maximum oxygen consumption minus rest; *Peak-Re*, peak exercise minus rest; *R10*, *R30*, and *R60-Re*, 10, 30, and 60 minutes recovery minus rest. *$P < .05$.

As expected, exercise capacity was reduced in heart transplant recipients (123 ± 12 vs 199 ± 14 W, $P < .001$). Resting plasma NOx values were increased after heart transplantation compared with normal values (56.3 ± 12.5 vs 27.0 ± 3.7 μmol/L, $P = .04$). Exercise increased plasma NOx values significantly in control subjects (+17.1% ± 5.6% [$P < .005$] and +19.4% ± 6.7% [$P < .02$] at 10 and 30 minutes of recovery, respectively), but plasma NOx values failed to change significantly in heart transplant recipients (Figure 1). Furthermore, confirming previous data,[3] a positive correlation was observed between both resting ($r = 0.96$, $P < .001$) and peak exercise ($r = 0.95$, $P < .001$) plasma NOx values and maximal power in healthy subjects. Such a relationship was lacking after heart transplantation (Figure 2).

Discussion

This study confirms that plasma NOx values increase during maximal exercise in healthy subjects and demonstrates for the first time that reduced exercise capacity is associated with reduced NO production, together with a loss of the NO-exercise capacity relationship after heart transplantation.

Previous studies demonstrated that exercise increases NOx, the release of which is stimulated by various local and circulating factors.

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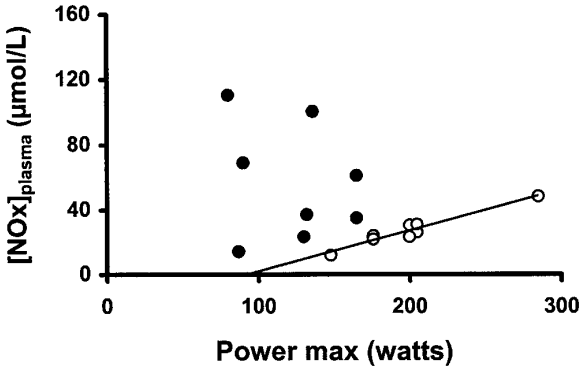

Figure 2. Relationship between resting plasma NOx values and maximal power in control subjects *(open circles)* and heart transplant recipients *(filled circles).*

The most important is shear stress, likely explaining exercise-induced NOx elevation in healthy subjects.[2,3] Although submitted to a similar hemodynamic stimulus, NOx values failed to increase in response to maximal exercise in heart transplant recipients. Several explanations may be proposed. First, according to previous data, resting NOx values were increased after heart transplantation compared with normal values.[5] Such elevation might subsequently reduce the ability of heart transplant recipients to further stimulate their NO pathway. This is nevertheless unlikely because increases of transient NOx values have been reported during rejection in heart transplant recipients.[5] Alternatively, exercise-induced NO production could be masked by a simultaneous enhancement in renal NO excretion after heart transplantation. Indeed, short-lasting plasma NOx variations result from both NO production and catabolism. Nevertheless, NO renal excretion is unmodified during exercise in normal subjects,[3] and if any effect, exercise should decrease NO renal excretion in heart transplant recipients in view of their greater decrease in renal blood flow at peak exercise. Thus, the lack of increase of NOx values in response to exercise after heart transplantation appears mainly related to an impaired NO production.

As in heart failure, peripheral factors are important determinants of exercise capacity after heart transplantation.[1,4] Particularly, peripheral vasoconstriction with reduced exercise-induced hyperemia to working muscles may be linked to endothelial dysfunction. Accordingly, heart transplant recipients not only present with an attenuated response to the endothelium-dependent vasodilator acetylcholine, but their impaired endothelial response closely correlates with their exercise capacity.[1] Our data support that besides an impaired endothelium-dependent vasodilation, a reduced endogenous NO production likely contributes to the lower peak exercise reached after heart transplantation. These mechanisms might lead to inadequate relaxation of smooth muscle in small arterioles and hypoperfusion to exercising muscles, explaining the loss of NOx-exercise capacity relationship observed after heart transplantation.

In summary, further expanding our comprehension of exercise limitation, we observed that besides the attenuated endothelium-dependant vasodilation of the microcirculation, reduced NO production might contribute to reduced exercise capacity in heart transplant recipients. This suggests the usefulness of studies investigating the effect of NO pathway stimulation on exercise capacity after heart transplantation.

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